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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/662,613	FARID ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-80* is/are pending in the application.

4a) Of the above claim(s) *11-24,27-43,46-50,52-56,65-70,72-74 and 76-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,25,26,44,45,51,57-64,71 and 75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/22/05; 5/21/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-80 are pending.
Claims 11-24, 27-43, 46-50, 52-56, 65-70, 72-74, 76-80 are withdrawn.
Claims 1-10,25,26,44,45,51,57-64,71 and 75 are examined on the merits.

Election/Restrictions

1. Applicant's election with traverse of Group VIII (methods to identify a pig comprising a SNP at position 3832 in the IGF-1R gene) in the reply filed on 6/31/2006 is acknowledged. The traversal is on the ground(s) that the different inventions do not require separate searches. This is not found persuasive because the different inventions are drawn to the analysis of different nucleic acid sequences from different animals and the searches of the sequences would not be coextensive. For example, a reference regarding a 12 bp deletion at positions 3896-3907 of the mouse IGF-1R gene (Group III) would not be expected to be a reference against a method requiring analysis of a SNP at position 3832 of the pig IGF-1R gene.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement, see for example pages 57-62 of the specification. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the

references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see for example pages 8, 11, 30 and 38. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112 - 2nd Indefiniteness

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-10 25, 26, 44, 45, 51, 57-64, 71, and 75 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

Claims 1-10 are drawn to a method for 'genetically identifying an animal with respect to its potential to reproductive longevity', however there is no method step in which any animal is in fact identified. It is thus unclear how the required method steps actually accomplish the purpose of the method as stated in the preamble of the claim.

Claims 25, 26, and 44 are drawn to a method of 'screening animals to determine those more likely to have reproductive longevity', however there is no method step in which a determination is made as to the 'reproductive longevity' of any animal. It is thus

unclear how the required method steps actually accomplish the purpose of the method as stated in the preamble of the claim.

Claims 45 and 51 are drawn to a method for 'screening animals to determine those more likely to exhibit favorable traits associated with reproductive longevity', however there is no method step in which a determination is made as to the 'favorable traits associated with reproductive longevity' of any animal. It is thus unclear how the required method steps actually accomplish the purpose of the method as stated in the preamble of the claim.

Claims 57-64 are drawn to a method for 'genotyping an animal', however there is no method step in which a determination is made as to the genotype of any animal. It is thus unclear how the required method steps actually accomplish the purpose of the method as stated in the preamble of the claim of 'genotyping an animal' where a genotype is typically described in the art of animal genetics as the nucleic acid content of an organism in both copies of a gene in a diploid organism.

Claims 71 and 75 are drawn to a method for 'genetically identifying an animal', however there is no method step in which any animal is in fact identified. It is thus unclear how the required method steps actually accomplish the purpose of the method as stated in the preamble of the claim.

6. Claims 1-10, 45, 51, and 57-64are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10 are unclear over recitation of the phrase 'with respect to its potential to reproductive longevity' in reference to identification of an animal, in claim 1. It is unclear if applicant intends to claim a method that provides indicia of an aspect of 'reproductive longevity', or a method that provides an identification regarding some other quality that may be related to 'reproductive longevity'.

Claims 45 and 51 are unclear over recitation of the phrase 'favorable traits associated with reproductive longevity' in claim 45. The term 'favorable' in claim 45 is a relative term which renders the claims indefinite (e.g. one might consider increased longevity favorable for an animal with other phenotypic traits that one is interested in propagating in a population, whereas one might consider increased longevity unfavorable for an animal with other phenotypic traits that one is particularly not interested in propagating in a population). The term 'favorable' is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Additionally, the phrase 'favorable traits associated with reproductive longevity' is indefinite because it is not clear if the method screens animals for 'reproductive longevity' or some other trait 'associated with reproductive longevity', thus the metes and bounds of the claim are indefinite.

Claims 57-64 are unclear over recitation of the term 'allele 2' in regard to the genotype of an animal. It is unclear if applicant intends to claim a particular genotype (e.g. specific nucleotide content at a specific position in a particular gene), or what is encompassed by the term 'allele 2'.

Claims 59 and 60 are unclear over recitation of the phrase 'prior to digesting the nucleic acid with a restriction enzyme' in claim 59 because there is no antecedent basis for the digestion of any nucleic acid with a restriction enzyme.

Claim 61 is unclear over recitation of the phrase 'the restriction enzyme is FokI' because there is no antecedent basis for any restriction enzyme in the claim.

Claim Rejections - 35 USC § 112 1st - Description

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-10,25,26,44,45,51,57-64,71 and 75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

The claims are drawn to methods for the analysis of nucleic acids and polymorphic nucleic acid markers in the insulin-like growth factor 1 receptor gene (IGF-1R) from animals wherein the polymorphisms are associated with reproductive longevity. The claims are thus broadly drawn to methods comprising the analysis nucleic acids that are indicative of reproductive longevity and encompass a multitude of different nucleic acid molecules of a wide variety of unique sequences.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis of a large number of nucleic acids comprising a wide variety of nucleic acid sequences. Claims 1, 2, 4-10, 25, 26, 45, 57-63, and 71 encompass the analysis of nucleic acids from any organism; claim 3 encompasses the analysis of mouse, pig, and cow, claims 44 and 51 encompass pig and mouse, claims 64 and 75 are drawn to pig. The claims are broadly drawn to any polymorphic variant of an IGF-1R gene (e.g. splice variants, polymorphisms and mutations including single and multiple nucleotide substitution, insertions, deletions, translocations and gene rearrangements); while claim 2 recites the polymorphism is selected from a SNP, a deletion, and an insertion, even the breadth of this limitation is noted, where, for example, an insertion can be an insertion of any number of nucleotides of any sequence. Additionally, claim 61 appears to be drawn to any polymorphism in the IGF-1R gene of any organism that either creates or removes any FokI restriction site anywhere within the gene. While claim 60 requires amplification of a nucleic acid with primers of SEQ ID NO: 21 and 22, the claims in fact encompass the detection of any polymorphism anywhere in the IGF-1R gene. Claim 62 encompasses any polymorphism of the IGF-1R gene of any animal which can give a restriction pattern with a 295 nucleotide fragment and a 55 nucleotide fragment, however because the claim contains no limitations regarding the structure or sequence of any primers used for amplification of the analyzed nucleic acid, claim 62 encompasses any polymorphism anywhere in the IGF-1R gene. Claims 71 and 75 are drawn to methods for identifying an animal comprising assaying for the presence of a genotype as set forth in SEQ ID

NO: 7 'or a region thereof' wherein the animal posses a sequence having '95% sequence identity to SEQ ID NO: 7 or a fragment thereof'. Claims 71 and 75 are thus broadly drawn to the detection of genotypes that need minimally comprise a fragment of the pig IGF-1R sequence set forth in SEQ ID NO: 7 and may contain any amount of any other nucleic acid sequence.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification discloses the nucleic acid sequence of the mouse IGF-1R gene (SEQ ID NO: 1) and the polymorphisms of an A to G substitution in intro 16, a G insertion in intron 16, a A to G substitution in exon 21, and a 12 bp –deletion in exon 21 (p.17; p.39 – Results; Fig 4 and 5; p.15-16). The specification also discloses the pig IGF-1R sequence (SEQ ID NO: 7) and 17 SNPs within the disclosed sequence (Fig 7; p.18; p.52). The instant specification does not disclose any IGF-1R sequences from any animals other than mouse or pig, nor any other polymorphic variants other than the aforementioned mouse and pigs polymorphisms.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, while the art teaches that there are many different polymorphisms in IGF-1R genes (e.g. NCBI dbSNP teaches that there are 569 SNPs identified in the mouse IGF-1R gene, and GeneCard output for

the human IGF-1R teaches that there are 991 SNPS in the human IGF-1R gene) the specification provides no guidance as to how one may identify IGF-1R polymorphisms other than the polymorphic variants particularly described in the specification. There is no guidance as to how to select a polymorphism with the required functionality (i.e. associated with reproductive longevity), as the specification does not provide for how one may *a priori* identify a polymorphism that is associated with reproductive longevity.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because of the small amount structural information regarding nucleic acid polymorphisms in the IGF-1R gene associated with reproductive longevity, one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed methods, regardless of the complexity or simplicity of the method of identification. Adequate written description requires more than a mere statement that analysis of such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acid sequences of the claimed methods is not deemed sufficient to reasonably convey to

one skilled in the art that Applicant is in possession of methods for analyzing the reproductive longevity of an animal by analysis of polymorphic markers in the IGF-1R gene.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Claim Rejections - 35 USC § 112 1st Enablement

9. Claims 1-10, 25, 26, 44, 45, 51, 57-64, 71 and 75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for methods of analyzing the reproductive longevity of an animal comprising assaying for the presence of a polymorphism in the IGF-1R gene.

Many of the claims are generic with regard to the animal which is analyzed and the polymorphism in the IGF-1R gene which is analyzed. While there may be other enabled specific embodiments of analyzed animals and polymorphic positions, consonant with the Election only methods for genetically identifying a pig comprising a SNP at position 3832 in the IGF-1R gene was specifically considered and discussed. All data was considered for the analysis of the generic claims.

While claims 71 and 75 do no recite a purpose for the claims method of genetically identifying an animal comprising assaying for the presence of a genotype in the IGF-1R gene, the claims are addressed in this enablement rejection consonant with the asserted use of such a method in identifying polymorphisms associated with reproductive longevity (p.5)

Nature of the invention and breadth of the claims

The claims of the instant application are drawn to methods for determining the reproductive longevity of an animal comprising analyzing polymorphisms in the IGF-1R gene.

Claims 1, 2, 4-10, 25, 26, 45, 57-63, and 71 encompass the analysis of nucleic acids from any organism; claim 3 encompasses the analysis of mouse, pig, and cow, claims 44 and 51 encompass pig and mouse, claims 64 and 75 are drawn to pig.

The rejected claims are drawn to the detection of a wide variety of polymorphic variants in the IGF-1R gene, encompassing an extremely large number of different types of polymorphisms (e.g. single base or multi-nucleotide transitions and transversions (including silent mutations), any single base or multi-nucleotide insertions or deletions and any type of gene rearrangement) anywhere within the IGF-1R gene (e.g. a coding, non-coding, or regulatory region of the gene). Claims 1, 2, 3, 4, 45, 51, 57, 59, 60, 63, and 64 have no limitations as to the nature of the detected polymorphism. Claims 5, 7-10, 25, 26, 44, 58 and 62 are broadly drawn to any polymorphism that can be detected by any change in a restriction digestion pattern; claim 61 is drawn to any polymorphism that creates or removes a FokI site. Claim 6 is

broadly drawn to any polymorphism that can be detected as a single strand conformational polymorphism (SSCP).

Claims 45 and 51 are broadly drawn to a method for screening animals to determine those more likely to exhibit 'favorable traits associated with reproductive longevity', thus the method is drawn to determining a variety of phenotypic traits.

Claims 71 and 75 are drawn to the detection of genotypes in the IGF-1R gene sequence that need only minimally comprise 'a region' of the sequence set forth in SEQ ID NO: 7. Thus the claims are drawn to the detection of any portion of the sequence set forth in SEQ ID NO: 7.

The nature of the claims requires the knowledge of an association between polymorphic variants of the IGF-1R gene sequence and the reproductive longevity of an animal.

Direction provided by the specification and working example

The specification teaches (Example 1, pages 35-52) the analysis of the mouse IGF-1R gene sequence in several mouse lines: control lines (C1 and C2); mouse lines selected for reproductive longevity with a standardized litter size of 8 (SA1 and SA2); and mouse lines selected for reproductive longevity without a standardized litter size (SU1 and SU2). The specification teaches that the mouse lines are established for reproductive longevity as measured by the average number of days from mating to the last parturition: e.g. 236, 265, and 159 days for SA1, SU1, and C1, respectively (p.36). The specification teaches that the sequence of IGF-1R gene from several individuals from each mouse line was analyzed (p.37 – source of DNA) and several polymorphic

positions within the sequence were identified (p.39 – Polymorphisms). The specification further teaches an analysis of the distribution of various alleles, genotypes, and haplotypes composed of the identified polymorphic markers in the individuals from the different mouse lines.

The specification also teaches an analysis (p. 52 – Example 2) of the IGF-1R gene sequence in ten pigs: Five living sows with high parity numbers and five animals culled for reproductive reasons representing high reproductive longevity and low reproductive longevity, respectively. And while the specification teaches that 'reproductive longevity' means a biologically significant increase in the number of pregnancies and/or the duration of time an animal is capable of reproduction, relative to the mean of a given population, group or species (p.16), the reference does not teach any particular numbers for the parity of the sows used in the example. The reference teaches the identification of five polymorphisms in the pig IGF-1R gene in the ten sows examined, and further teaches that each polymorphism was assayed over a larger sample of animals from the same population to look for evidence of an association with increased reproductive longevity. The specification does not provide any details about this subsequent examination, or any results pertaining to the study.

The specification further teaches an analysis of a polymorphism (indicated as 'SNP 3832'; a C to T change at position 4889 of SEQ ID NO: 7; Figure 7C) in pigs (Example 3, p.55-56). The specification asserts that 'Allele 2' of the gene (T at position 4889 of SEQ ID NO: 7; presence of a FokI site in an fragemtn amplified with SEQ ID NO: 21 and 22) is positively associated with longevity. However, the specification

indicates that in an analysis of 996 sows from four different farms, the determine effect is overestimated due to the data structure (p.55, lines 10-11). Example 3 further teaches the association of 'Allele 2' in boars and increased numbers of parities from the sows sired by the boars 'Allele 2'. The specification asserts that there is a positive association between sow homozygosity and reproductive longevity (p=0.062), but the specification does not teach that the genotypes of any of the sows in this second study of SNP 3382 was in fact determined.

While the specification asserts that the analyses of IGF-1R sequences in mice is applicable to the livestock industry, including dairy cattle (p.42), the specification does not teach any analysis of any IGF-1R gene sequences other than those in pig and mouse.

The specification does not teach any analysis of an association of particular IGF-1R sequences with any traits other than the average number of days from mating to the last parturition in mouse (Example 1), and number of parities and days to culling for reproductive performance in pig (Example 3).

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection of any particular nucleic acid sequence, or the detection of a polymorphism in a particular sequence is high, the level of unpredictability with regard to associating the presence of a nucleic acid sequence or any particular polymorphism with a phenotype, such as a a measure of reproductive longevity, is even higher. The unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Because the claims encompass the determination of reproductive longevity by analysis of any polymorphism in the IGF-1R gene of any organism, it is relevant to point out that the art with regard to IGF-1R polymorphisms teaches the breadth of such polymorphisms. NCBI dbSNP teaches that there are 569 SNPs identified in the mouse IGF-1R gene, and GeneCard output for the human IGF-1R teaches that there are 991 SNPS in the human IGF-1R gene; the vast majority of these polymorphisms are not discussed by the specification nor taught by the prior art as being associated with reproductive longevity.

Because the claims encompass methods for determining animals likely to exhibit favorable traits 'associated with reproductive longevity', it is relevant that the post-filing art of Moeller et al (2004) teaches a number of traits that are associated with reproductive productivity (Table 2) for which the specification provides no analysis.

The prior art teaches the unpredictability of using nucleic acid sequence analysis for the determination of a phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627). Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the

finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph).

Even in cases where an association between a particular gene and a phenotypic state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using polymorphism analysis it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi (1998)). Furthermore, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be phenotype-associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p-value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for mutations within the same gene, it is highly unpredictable as to whether a particular mutation will be associated with a phenotype.

While the claims encompass the analysis of any organism, it is relevant to point out the unpredictability with regard to analyzing genetic elements among different species. While it is generally held true that structure correlates with function, Bork et al (1993) teaches an analysis of sugar kinases, and indicates that very distinct proteins (with different three-dimensional structures and strikingly different sequence patterns)

can catalyze chemically equivalent reactions of similar or identical substrates (p.31 - Abstract). Additionally, sequences that appear quite similar may in fact have very different functionalities. Such a possibility is exemplified by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S). Thus it is highly unpredictable as to how one would extrapolate methods or results regarding association of any particular IGF-1R polymorphism with reproductive longevity in any one animal with any association in any other different animal.

And while the specification asserts an association between the T allele of SNP 3832 and reproductive longevity in the two studies of Example 3, it is relevant to point out that the specification indicates the reported result from the first analysis (using 996 sows) is questionable because of the data structure (p.55, lns. 10-11). It is also relevant to point out that the analysis of the pig IGF-1R sequence presented in Example 2 does not teach the identification of this position as polymorphic in the pigs examined in Example 2. Additionally, the data presented for the second analysis (using over 19,000 sows from 179 sires) indicates as association with a p-value of P=0.062. Thus, while the prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion) the

instant specification does not teach consistent and significant correlation of SNP 3832 with reproductive longevity in pigs. Additionally the analysis of Example 1 demonstrates the unpredictability of associating a genotype of SNPs in the IGF-1R gene with reproductive longevity in mouse. For example, the example teaches that in juvenile mice, there is not a consistent statistically significant association between reproduction longevity and the genotype at the 'A' site of IGF-1R (A to G substitution in intron 16) in the SA1, SA2, or SU1 mice examined (Table 5).

It is noted that none of the claims particularly require the analysis of the nucleotide content of the pig IGF-1R gene at the SNP 3832 position. Claims requiring amplification with specific primers (claim 60) do not requires analysis with any particular restriction enzyme. Claims requiring a particular restriction enzyme for digestion (claim 61) do not require the use of any particular primers for amplification of a PCR product, and claims that require a particular restriction fragment pattern (claim 62) do not require any particular enzyme for digestion or primers for amplification of a PCR product. Even if a claim did require amplification with SEQ ID NO: 21 and 22, digestion with FokI, and a restriction pattern with a 292 bp and 55 bp product (specification example 3, pages 55-56), it is noted that there are a multitude of mutations that could yield the required restriction pattern. Because the FokI enzyme cuts outside of its required recognition sequence (i.e. GGATG(9/13)), the creation of a FokI site at any one of four different locations in the PCR product created by amplification with SEQ ID NO: 21 and 22 would yield indistinguishable restriction patterns. Thus even a claim drawn to digestion with FokI of an amplification product created using SEQ ID NO: 21 and 22 to yield 292

and 55 base pair products would not sufficiently define the specific location and identity of the SNP 3832 mutation of the instant specificaiton.

Quantity of experimentation required

A larger and prohibitive amount of experimentation would be required to make and use the claimed invention. One would first have to identify any polymorphic position in the IGF-1R gene of any animal. One would then have to perform case:controlled studies with a large number of animals to determine a statistically significant association between any particular polymorphism and reproductive longevity (as determined by a significant increase in the number of pregnancies and/or the duration of time an animal is capable of reproduction, relative to the mean of a given population, group or species) as well as an association with any traits associated with reproductive longevity.

And although as currently written none of the claims specifically require an analysis of the nucleotide content at the SNP 3832 position, because the specification does not clearly teach a consistent and significant association of this position with reproductive longevity, one would have to perform an analysis of this polymorphic position in any particular pig population of interest to determine whether or not it is associated with reproductive longevity.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the

specific working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the claimed invention.

Claim Rejections - 35 USC § 102

In the rejection of claims under 35 USC 102, as noted in the MPEP 211.02, 'a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone'. Further, in Pitney Bowes Inc. v. Hewlett-Packard Co., 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, 'then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation'.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-4, 25, 26, 44, 45, 51, 57, 63, 64, 71, and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Harumi et al (2001 as cited in the IDS).

Harumi et al teaches an analysis of the pig IGF-1R gene sequence using RT-PCR analysis of the cDNA sequence, and the identification of polymorphic positions within the sequence.

Regarding claim 1, the reference teaches a method comprising obtaining a sample of genetic material from an animal (p.386, right column, first paragraph), and assaying for the presence of a polymorphism in the IGF-1R gene sequence (p.388, left col.; Fig 2). Regarding the requirement that the polymorphism is associated with

reproductive longevity, the reference teaches the detection of the C/T polymorphism at position 3832. If applicant asserts that the SNP 3832 is associated with reproductive longevity, then this association is an inherent property of the polymorphism.

Regarding claim 2, the reference teaches the single nucleotide polymorphism at position 3832 (Figure 2).

Regarding claim 3, the reference teaches the analysis of the IGF-1R gene sequence from a pig.

Regarding claim 4, the reference teaches assaying for the polymorphism by direct sequencing (p.388, left col.).

Regarding claim 25, the reference teaches a method comprising obtaining a sample of genetic material from an animal (p.386, right column, first paragraph), and analyzing the nucleic acid content of the IGF-1R gene, thus assaying for the presence of a genotype (p.388, left col.; Fig 2). Regarding the requirements that the genotype is associated with reproductive longevity and characterized by a restriction fragment pattern, the reference teaches the analysis of the nucleotide content and the SNP 3832 position. Association with reproductive longevity and characterization by a restriction fragment pattern are inherent properties of this polymorphic position.

Regarding claim 26, the reference teaches amplification of a gene region comprising the polymorphic position, which is a marker, using forward and reverse primers (Fig 1).

Regarding claim 44, the reference teaches the analysis of the IGF-1R gene sequence from a pig.

Regarding claim 45 the reference teaches a method comprising obtaining a sample of genetic material from an animal (p.386, right column, first paragraph), and detecting the presence at least one allele in the IGF-1R gene (p.388, left col.; Fig 2). Regarding the requirement that the presence of the allele is predictive of the animal having reproductive longevity, the reference teaches the detection of the C/T polymorphism at position 3832. If applicant asserts that the SNP 3832 is predictive of reproductive longevity, then the predictive nature of this allele is an inherent property of the polymorphism.

Regarding claim 51, the reference teaches the analysis of the IGF-1R gene sequence from a pig.

Regarding claim 57, the reference teaches a method comprising obtaining a sample of genetic material from an animal (p.386, right column, first paragraph), and detecting a polymorphism in the IGF-1R gene of the animal (p.388, left col.; Fig 2). Because the reference teaches analyzing the sequence of the IGF-1R gene by sequencing of an RT-PCR product, determining the nucleotide content a the indicated position is a determining a marker for the allele, and the reference teaches determining homozygosity of certain animals (for example for the SNP at position 3832 in the Landrace 1 sample of Fig 2), thus the marker is indicative of two copies of allele 2.

Regarding claim 63, the reference teaches detecting homozygosity of an animal for the 'T' allele of the 3832 SNP. If applicant asserts that this allele of SNP 3832 is positively associated with reproductive longevity, then this positive association is an inherent property of the polymorphism.

Regarding claim 64, the reference teaches the analysis of the IGF-1R gene sequence from a pig.

Regarding claim 71, the reference teaches a method comprising obtaining a sample of genetic material from an animal (p.386, right column, first paragraph). The reference further teaches determining a genotype of the IGF-1R gene by sequence analysis of the pig IGF-1R gene and indicates that the sequence of the gene includes the sequence of GenBank Locus: AB003362 (bottom of Fig 2). The sequence analysis of the coding region of the pig IGF-1R as taught by Hurim et al thus assays for the presence of a region of the sequence as set forth in SEQ ID NO: 7, and the analyzes animals posses a nucleic acid sequence having at least 95% sequence identity to a fragment of SEQ ID NO: 7 (as evidence by GenBank GI:11182406 and the provided alignment 'ALIGN GI:11182406 – SID7'). For example, the sequence of positions 3814-3873 of AB003362 is a fragment with at least 95% identity to positions 4871-4930 of SEQ ID NO: 7.

Regarding claim 75, the reference teaches the analysis of the IGF-1R gene sequence from a pig.

It is noted that this rejection of claims under 35 USC 102 cites multiple references. However, the additional references (GenBank GI:11182406 and the provided Alignment of 'ALIGN GI:11182406 – SID7') are cited as they provide evidence of the inherent characteristics of the method of Harumi et al, specifically that the methods taught by Lucy et al comprise a sequence corresponding to a fragment of the sequence set forth in SEQ ID NO: 7 (see MPEP 2131.01).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Harumi et al (2001 as cited in the IDS) in view of Larsen et al (2001).

Harumi et al teaches a method comprising obtaining a sample of genetic material from an animal (p.386, right column, first paragraph), and assaying for the presence of a polymorphism in the IGF-1R gene sequence (p.388, left col.; Fig 2). Regarding the requirement that the polymorphism is associated with reproductive longevity, the reference teaches the detection of the C/T polymorphism at position 3832. If applicant asserts that the SNP 3832 is associated with reproductive longevity, then this association is an inherent property of the polymorphism. The reference also teaches assaying for the polymorphism by direct sequencing (p.388, left col.). Thus Harumi et al teaches all of the limitations of claims 1 and 4, from which the rejected claim 6 depends.

Harumi et al does not teach a method wherein the step of assaying the polymorphism is SSCP.

Larsen et al teaches the analysis of sequence mutations using SSCP analysis (p.388, right col., Description of the techniques).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the polymorphisms of Harumi et al using the SCCP method as described by Larsen et al. One would have been motivated to use the SSCP method of Larsen et al because Larsen et al teaches the successful analysis of mutaitons using SSCP (p.388, right col., lns. 38-40), and thus the method would provide alternative methods for the analysis of SNP positions of interest.

Conclusion

14. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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